Phase 1 Clinical Trial of TN-301, a Highly Selective HDAC6 Inhibitor With Potential in Heart Failure With Preserved Ejection Fraction (HFpEF), Shows Target Engagement

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TN-301 is well tolerated over a wide dose range, with dose-dependent increase in target engagement, generally dose-proportional increase in exposure, and a half-life consistent with once-daily dosing, showing promise as a potential pharmacologic therapy for HFpEF

INTRODUCTION

- Heart failure with preserved ejection fraction (HFpEF) is associated with high morbidity and mortality, and remains a major health concern[1]
- TN-301 (TYA-11631) is a highly selective inhibitor of histone deacetylase 6 (HDAC6), an important factor in coordinating cellular processes within the cell cytoplasm[2]
- Assessment of HDAC6 inhibition in multiple preclinical models has demonstrated cardioprotective properties, with a distinct, multimodal mechanism of activity, including direct effects on the heart and systemic effects on pathways linked to HFpEF pathogenesis, while avoiding undesirable effects of broader HDAC inhibition[2,3]
  - Direct effects observed include decreased hypertrophy, improvements in diastolic function, reduced fibroblast activation and enhanced cellular metabolism
  - Systemic effects of HDAC6 inhibition include improvement in mitochondrial dysfunction, fibrosis and inflammation[2]
  - Co-administration of highly selective HDAC6 inhibitors with empaglifozin showed additive benefits in preclinical HFpEF models via orthogonal mechanisms of action (HFSA 2023; Poster #104; Control #1769)
- This first-in-human Phase 1 study was designed to evaluate safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of TN-301 in healthy participants and to inform dose ranges for future studies in HFpEF patients

METHODS

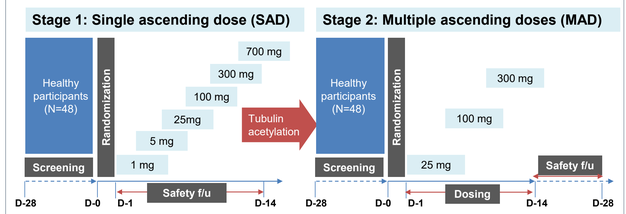
Participants

- Healthy adults (women and infertile men*), 18 – 60 years of age, with informed consent

Study Design

- This was a 2-stage randomized, blinded, placebo-controlled study (**Figure 1**)
  - A single ascending dose (SAD) stage evaluated 6 dosing cohorts (1 mg – 700 mg)
  - Demonstration of target engagement (measured by tubulin acetylation in circulating PBMCs) was required to define the initial dose in the second stage of the study
  - The multiple ascending dose (MAD) stage evaluated once-daily dosing at 25 mg, 100 mg or 300 mg for 14 consecutive days
  - Each cohort had 8 participants (6 TN-301 and 2 placebo-treated)
- Dosing in each SAD cohort was initiated with a sentinel pair (1 placebo, 1 TN-301) at least 24 hours before dosing of remaining participants in that cohort

Figure 1. Phase 1 Study Design of TN-301 in Healthy Participants



Starting dose in Stage 1 of study was determined from IND-enabling nonclinical toxicology studies

Study Conduct

- The study was conducted per protocol, at a single US site
- All enrolled participants completed the study and safety follow-up without any drop-outs

RESULTS

Baseline Characteristics

- A total of 48 participants (TN-301 = 36 | placebo = 12) enrolled in stage 1 (SAD) and 24 participants (TN-301 = 18 | placebo = 6) in stage 2 (MAD) (**Table 1**)

*Fertile men were excluded from the study, out of abundance of caution, due to a finding in nonclinical studies. Relevance of this finding to humans is not known.

RESULTS (continued)

Table 1: Baseline characteristics

	SAD cohorts N=48	MAD cohorts N=24
Age, mean years (SD)	41.2 (10.0)	41.3 (8.9)
Sex,* n (%)		
Male	4 (8.3)	4 (16.7)
Female	44 (91.7)	20 (83.3)
Race, n (%)		
Asian	1 (2.1)	1 (4.2)
Black or African American	15 (31.3)	9 (37.5)
White	32 (66.7)	14 (58.3)
Weight, mean kg (SD)	73.7 (11.1)	76.2 (10.9)
BMI, mean kg/m^2 (SD)	27.7 (3.2)	28.6 (3.3)

Safety and Tolerability of TN-301

- TN-301 was well tolerated at the doses evaluated
- No serious adverse events or dose-limiting toxicities were reported
- Frequency of adverse events (AEs) in TN-301-treated participants did not increase with dose
- Findings in SAD and MAD stages of the study were largely similar; AEs in MAD stage are summarized below (**Table 2**)
- Most frequent AEs observed were related to GI disturbance
- Frequency of GI AEs were similar between TN-301- and placebo-treated participants, and across dose groups, suggesting that such findings were likely due to the vehicle used to administer TN-301 or placebo
- TN-301 did not result in any concerning patterns of cardiovascular AEs (including on telemetry, ECGs, and vital signs) across the dose ranges evaluated
- TN-301 administration did not result in hematologic findings as have been reported with other HDAC6 inihibitors[4]
- AEs of dizziness and blurred vision were considered not related to study drug

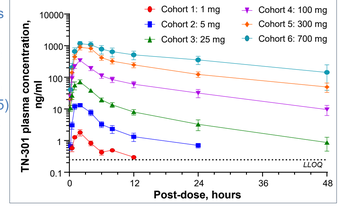
Table 2: Summary of AEs Reported in Two or More Participants in MAD Stage

Preferred term, n (%)	25 mg TN-301 n=6	100 mg TN-301 n=6	300 mg TN-301 n=6	Placebo n=6
Any AE	**5 (83)**	**5 (83)**	**6 (100)**	**6 (100)**
Diarrhea	4 (67)	5 (83)	4 (67)	3 (50)
Flatulence	3 (50)	4 (67)	2 (33)	3 (50)
Procedural pain	4 (67)	3 (50)	3 (50)	2 (33)
Nausea	3 (50)	3 (50)	0	1 (17)
Abdominal pain	1 (17)	4 (67)	0	1 (17)
Headache	4 (67)	0	1 (17)	1 (17)
Pruritus	0	4 (67)	1 (17)	0
Dermatitis contact	1 (17)	0	3 (50)	0
Dizziness	1 (17)	0	1 (17)	0
GI sounds abnormal	1 (17)	0	0	1 (17)
Vision blurred	0	2 (33)	0	0

Pharmacokinetics - SAD

- Plasma exposure generally increased proportionally with TN-301 dose across the dose ranges evaluated (**Figure 2**)
- At doses where the concentration-time profile was fully characterized (25 mg – 700 mg), terminal elimination half-life ranged from 8.13 hr (SD ± 2.95) to 14.6 hr (SD ± 6.04), suggesting that once-daily dosing was appropriate for MAD stage of the study

Figure 2. Mean (SEM) plasma TN-301 concentration over time (SAD)



RESULTS (continued)

Pharmacokinetics - MAD

- Exposure increased with once-daily dosing at each dose evaluated (**Figure 3**); reaching steady state by approximately Day 10
- Mean (±SD) terminal half-life after last dose ranged from 9.27 hr (±1.5) to 13.7 hr (±3.35) suggesting that once-daily dosing remains appropriate for future clinical trials (**Table 3**)

Figure 3. Mean (SEM) plasma TN-301 concentration over time (MAD)

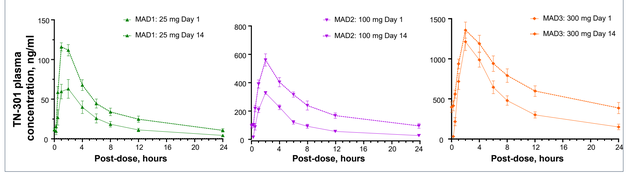


Table 3: Summary of TN-301 PK Parameters (Day 14) from MAD Stage of Phase 1 Study

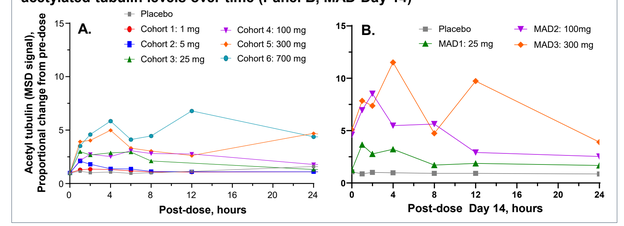
Dose (mg)	Cmax, ss (ng/mL)	Tmax, ss (hr)	$AUC_{tau,ss}$ (h*ng/mL)	Half-life, ss (hr)	Accumulation Ratio
25	**116** (11.6)	**1.01**	**824** (28.6)	**9.27** (1.5)	**1.97** (15.6)
100	**552** (20.6)	**2**	**5120** (26.7)	**11.1** (2.43)	**2.36** (25.7)
300	**1340** (18.4)	**2**	**16300** (24)	**13.7** (3.35)	**1.62** (14.3)

C_{max}, AUC, accumulation ratio shown as geometric mean and geometric CV
T_{max} shown as median values; half-life shown as arithmetic mean and SD

Pharmacodynamics – SAD + MAD

- Acetylated tubulin levels in peripheral blood mononuclear cells (PBMCs) from TN-301 treated participants were higher than those in placebo-treated participants starting at doses as low as 5 mg (**Figure 4A**) indicating engagement with HDAC6 target
- Maximal acetylated tubulin levels increased with TN-301 dose (**Figure 4A**) suggesting robust dose-dependent target engagement
- Maximal acetylated tubulin levels on Day 14 were higher than those on Day 1 (**Figure 4B**)
- Duration of effect at higher SAD doses and in MAD stage lasted 24-48 hrs (**Figure 4A, B**)
- In mouse HFpEF models, maximal efficacy was observed at 3 mg/kg; which corresponded to about half of maximal acetylated tubulin levels[5]
- In addition, in mouse models, acetylated tubulin levels above baseline were required for 6-8 hrs post-dose to reach maximal efficacy; NOT throughout 24 hr dosing interval[5]
- Therefore, TN-301 doses approximately in the low-to-mid range evaluated in this study (approximately 25 mg – 100 mg once daily) may meet or exceed plasma exposures and target engagement observed preclinically for maximal efficacy

Figure 4. Mean acetylated tubulin levels over time (Panel A, SAD-Day 1) and mean acetylated tubulin levels over time (Panel B, MAD-Day 14)



Variability (SEM) in acetylated tubulin levels ranged from 0.038 to 1.410 (SAD results); and 0.067 to 4.050 (MAD results)

RESULTS (continued)

Pharmacodynamics - continued

- Increasing TN-301 exposure correlated with increasing pharmacodynamic effect (**Figure 5**)
- No changes or trends in acetylated histone relative to pre-dose were observed in any SAD or MAD cohorts (**Figure 6**)

Figure 5. Acetylated tubulin AUC increased with TN-301 AUC (SAD + MAD)

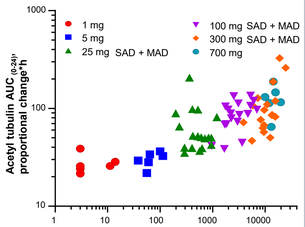
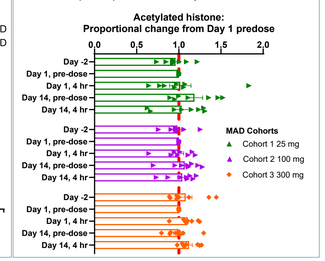


Figure 6. No change in mean acetylated histone (SEM) relative to predose in MAD



CONCLUSIONS

- TN-301 is a highly selective, orally bioavailable HDAC6 inhibitor under development as a potential treatment for patients with HFpEF
- TN-301 is well tolerated in healthy adult participants after single (1 mg - 700 mg) and multiple once-daily doses (25/100/300 mg x 14 d)
- Adverse events observed were of similar frequency between TN-301 treated and placebo groups
- Frequency of AEs did not increase with TN-301 dose
- TN-301 dosing did not change activity of other HDAC isoforms; distinguishing this agent from other HDAC6 inhibitors[4]
- Plasma exposure generally increased proportionally with TN-301 dose
- Robust HDAC6 inhibition (target engagement) noted; acetylated tubulin levels increased TN-301 doses starting at doses as low as 5 mg
- Plasma exposures and target engagement observed in this study met or exceeded those observed preclinically at or near maximal efficacy
- Results of this study support further evaluation of TN-301 in HFpEF patients with once-daily dosing (roughly in 25 mg – 100 mg dose range)

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5. Data on file at Tenaya

ACKNOWLEDGEMENTS

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